TABLE 4.—Smoking habits of 21 Navajo uranium miners with lung cancer

Cigarettes/day	Number of men
0.0	8
<1	2
1–3	6
4–8	5

SOURCE: Adapted from Samet, Kutvirt et al. (1984).

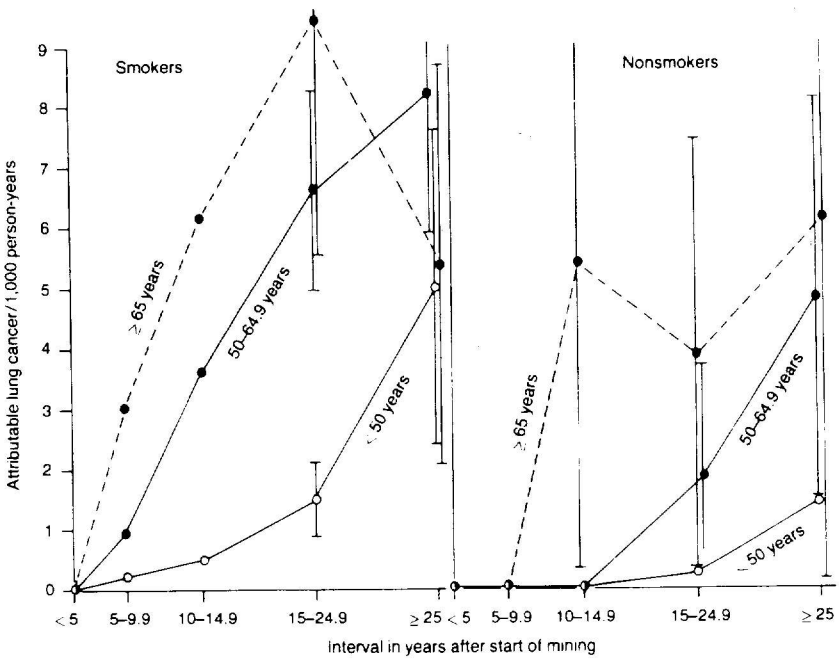

FIGURE 2.—Influence of age at observation and induction-latent period on attributable lung cancer deaths among U.S. uranium miners

NOTE: Error bars are 90 percent confidence intervals.
SOURCE: Adapted from Roscoe et al. (in press).

birthdate, on year when their mining started, and on the magnitude and rate of exposure to radon daughters. The mean I-L period was 23.9 and 18.5 years for nonsmokers and smokers, respectively

($p < 0.001$). The mean age at death was 54.7 and 50.2 years, respectively ($p < 0.001$).

Two sophisticated analyses using Cox regression methods were done of the U.S. uranium miner cohort in an attempt to determine the relative contribution of various factors to the miners' lung cancers. One of the analyses used a cohort approach (Hornung and Samuels 1981); the other used a nested case–control approach (Whittemore and McMillan 1983). Both concluded that the interaction between smoking and radiation effects was multiplicative.

Swedish Miners

Axelson and Sundell (1978) conducted a case–control study of lung cancer patients in the area around two adjacent lead-zinc mines that had begun operating prior to 1920. Twenty-nine lung cancer cases were identified from parish death register data; the controls were the three individuals entered in the register just before and just after each lung cancer case, but who had not died of lung cancer. Of the 29 cases, 21 had underground mining exposure in comparison with only 19 of the 174 controls. The mean radon daughter exposure of the lung cancer cases was approximately 300 WLM. Smoking information was obtained for both groups (some from relatives). Data on the 21 lung cancer deaths of miners were collected over a 20-year period (1956–1976). The mean age at death was 70 and 59 years, respectively, for nonsmokers and smokers with lung cancer. The mean I-L period was 43 and 34 years, respectively, for nonsmokers and smokers with lung cancer. The nonsmokers contributed 47 percent of the lung cancers, whereas only 19 percent of the controls were nonsmokers.

Damber and Larsson (1982; Larsson and Damber 1982) performed a case–control study of 604 male lung cancer deaths in the three northernmost counties of Sweden. Two control groups were selected from among deceased and living populations. Decedent controls were drawn from the national registry for causes of death and matched for sex, year of death, and municipality to the lung cancer cases. Living controls were selected only for those lung cancer cases under the age of 80 (467 cases) and were drawn from the national population registry and matched for age, sex, and year of birth. Twenty-five of the cases and only 10 of the controls had underground mining exposure. The relative risks for smoking and underground mining exposure were these: nonsmoking individuals with no underground mining exposure, 1; nonsmokers with underground mining exposure (2.4 decedent controls, 7.0 living controls); smokers with no underground mining exposure (6.8 decedent, 7.4 living); and smoking miners (18.2 decedent and 16.1 living). The mean age at death was 69 and 63 years, respectively, for nonsmokers and smokers among the miners with lung cancer. The mean I-L period was 43 and 35 years,

respectively, for nonsmokers and smokers among the miners with lung cancer. The mean exposure was not given, but was probably about 100 WLM, as many of the subjects were the individuals studied by Radford and Renard (1984). This difference was considered to represent a multiplicative effect of cigarettes and radon daughters, but it was not possible to rule out an additive effect.

Case–control studies were done with a different group of Swedish iron miners (Edling 1982; Edling and Axelson 1983). Cases were deaths from lung cancer, and controls were miners who died from nonmalignant causes, matched for birthdate, sex, and year of death. Mean exposures were about 100 WLM. There were 44 cases among miners, and a standardized mortality ratio (SMR) of 11.5 to 16.2 was calculated for lung cancer. Of these 44 cases, 38 were smokers and 6 were nonsmokers. The risk ratio was 1.5 to 2 times greater among smokers than among nonsmokers. The mean age at death was 67 and 61 for nonsmokers and heavy smokers, respectively. The mean I-L period was 40 and 37 for nonsmokers and heavy smokers, respectively. The authors concluded that the interaction was probably additive.

A retrospective cohort study was done of another group of workers from two iron mines, one worked since 1890, the other since 1920 (Radford and Renard 1984). Death data were collected for a 26-year period (1951–1976). There were 50 lung cancer deaths that occurred 10 or more years after start of mining. The mean exposure was about 94 WLM (84 WLM corrected for exposure immediately prior to death). Smoking information was obtained from relatives for all lung cancer deaths and by questionnaire from approximately half of those study members alive in 1973. Using general population data on smoking and mortality, a dose–response relationship for radon daughter exposure was demonstrated. There were 18 lung cancer deaths among nonsmokers versus 32 among smokers. The relative risk due to radon daughter exposure was 10 for nonsmokers and 2.9 for smokers ($p < 0.001$), and the radiation exposures were approximately equal for both groups. The absolute excess lung cancer risk attributable to radon daughter exposures was slightly higher for smokers than for nonsmokers. The mean I-L periods were 41.3 for nonsmokers and 38.8 years for smokers. The mean age at death from lung cancer was approximately 65 years, but was not calculated by smoking status. The authors concluded that the interaction was slightly more than additive.

Canadian Miners

In studies of a group of Canadian fluorspar miners there were only 2 lung cancer deaths among nonsmokers versus 76 among smokers (Wright and Couves 1977; Morrison et al. 1981). Smoking data were incomplete, but it was estimated that only 5 percent of the miners were nonsmokers. The mean exposure was approximately 600 WLM.

The followup period was from 1933 to 1977, an interval of 44 years. The mean I-L period was 25 years and declined with increasing age at start of mining. The mean age at death was 52 years.

An analysis of sputum cytology results from 249 active Canadian uranium miners found that the frequency of atypical cells in sputum was related to both cigarette smoking and radiation exposure. Few atypias were seen among nonsmokers, and this was interpreted as a potentiation of the radiation effect by smoking (Band et al. 1980).

Other Epidemiological Studies Relating Radiation and Cancer

Because of the high cost of imported fuel, the Swedes were among the first to emphasize the closing of cracks and adding insulation to dwellings in order to conserve heating fuel. Sealing the indoor environment also resulted in an elevation in the radon levels in the indoor environment. These radon exposures have resulted in a substantial interest in Sweden in the role of radon as well as in the role of cigarette smoking on their lung cancer death rates.

A case–control study was conducted in rural areas of Sweden, limited to people who had lived at the same address for 30 years before death (Axelson 1983). Measurements of radon in different types of houses led the researchers to classify wooden houses without basements as low radon, and brick or concrete houses with basements (especially those built on alum shale or granite deposits) as high radon. Smoking histories were obtained on half of the cases from questionnaires completed by relatives. In the high exposure housing, smokers had a lung cancer crude risk ratio of 8.3; in the low exposure houses the ratio was only 2.0. There was no difference in smoking habits between inhabitants of the two types of houses. The researchers felt that this indicated a multiplicative or synergistic interaction. A second study of Swedish residents did not alter that conclusion (Axelson 1983; Edling et al. 1984).

In a case–control autopsy study of 204 Japanese A-bomb survivors with lung cancer who subsequently died, the relationship of smoking to radiation exposure was examined (Ishimaru et al. 1975). An increase in lung cancer risk was seen with increasing radiation exposure and increasing amount smoked, but no interaction could be discerned.

A cohort study of 40,000 A-bomb survivors studied the relationship of cigarette smoking and radiation exposure to cancer mortality (Prentice et al. 1983). Subjects were stratified by smoking and radiation categories, and multiplicative and additive models were examined. There were 281 lung cancers. The lung cancer risk rose with both increasing radiation and increasing smoking. Cancer of some sites showed an absence of or a negative correlation, but both esophageal and lung cancer risk rose with both increasing radiation

TABLE 5.—Interaction of radiation and cigarette smoking among Japanese A-bomb survivors

Cancer site	Number of cancers	Relative risk estimates					
		Nonsmokers			Smokers		
		< 10 rad	10–99 rad	≥ 100 rad	< 10 rad	10–99 rad	≥ 100 rad
Stomach	658	1	1.2	1.4	1.3	1.0	1.3
Esophagus	58	1	3.2	6.5	5.6	6.6	7.8
Lung	281	1	1.1	2.3	2.4	2.4	3.6

SOURCE: Adapted from Prentice et al. (1983).

and increasing smoking (Table 5). The use of Cox regression analysis did not distinguish between an additive or a multiplicative interaction.

Preliminary findings from a case–control study among A-bomb survivors suggest that gamma radiation and cigarette smoking combine in an additive fashion to increase lung cancer risk (Blot et al. 1984).

Comment on Epidemiological Studies

With the exception of some of the U.S. studies with over 300 lung cancer cases, most of the human studies were of relatively small populations, with small numbers of lung cancers. Although confidence in the risk estimates and the mean I-L periods derived is decreased, there is no reason to suspect that the small population sizes provided any qualitative distortion of the smoking–radiation interaction. The studies varied in the quality of their radiation dose estimates and of their smoking information. Some of the smoking data was obtained by interview, some retrospectively from relatives, and some at entry into the study with no consideration given to subsequent changes in smoking habits. Because of the small numbers, pipe and cigar smokers and ex-smokers were sometimes combined with other groups or light smokers and heavy smokers were often combined. Some had smoking information on little more than half of the population. The observations of protective, additive, or multiplicative effects cannot be easily dismissed. These observed differences could all be correct for specific groups at specific times without violating any biological principles.

The mean I-L periods in the various studies differ considerably, as do the relationships between nonsmoker and smoker I-L periods. It should be noted that in all of the studies the I-L period was shorter among smokers than among nonsmokers, although in some studies

the difference was small. In studies of radiation and cancer, it has frequently been noted that the observed latent period is strongly dependent on age at exposure and on the length of the followup period. That is, subjects who are young at first exposure and who are followed for most of their lives will exhibit a much longer mean latent period than will a group first exposed during middle age and followed for only 25 years. The intensity and magnitude of exposure may also have an influence on the I-L period (Archer et al. 1979). Longer I-L periods were noted among Europeans than among U.S. miners. Longer followup periods and higher radiation dose rates and doses are probably responsible for this difference.

Cigarette smoking habits may also influence the measured I-L period for developing lung cancer following onset of radon daughter exposure independent of any biologic interaction. Even without significant radon daughter exposure, a number of smoking miners would have developed lung cancer, and some may have done so prior to the latent period required for radiation-induced cancers. This phenomenon would be particularly important in those individuals whose radiation exposure (but not their smoking exposure) began late in life. The effect of this independent development of lung cancer due to cigarette smoking would be to shorten the I-L time calculated for radon daughter exposure in smokers compared with nonsmokers, and for workers who joined the workforce later in life compared with those whose exposure began at a younger age.

Differences in age at start of mining and years of followup between the nonsmokers and smokers within a cohort might well influence the relative risks calculated for the two subgroups within any study. However, even if age at start, years of followup, and percentage ultimately developing lung cancer are the same for nonsmoking and smoking subgroups, their relative frequency of induced lung cancer might vary considerably with time, as indicated in Figures 2 and 3.

Interaction of Radiation and Cigarette Smoke (or Its Constituents) in the Generation of Animal Tumors

A number of animal experiments have explored the possible interactions between cigarette smoke or cigarette smoke condensate (CSC) and ionizing radiation. These experiments have used x-ray or alpha or beta radiation. Some have used rat or mouse skin as the test object; others have used the lungs of living animals.

Bock and Moore (1959) found that intense x-ray exposure of a small portion of the mouse body increased the sensitivity of distant areas of the skin to cancer induction by painting with CSC.

An experiment using CSC and beta radiation from ^{90}Sr on mouse skin (400 mice) was reported at two separate time points (Suntzeff et al. 1959; Cowdry et al. 1961). In this experiment both the beta

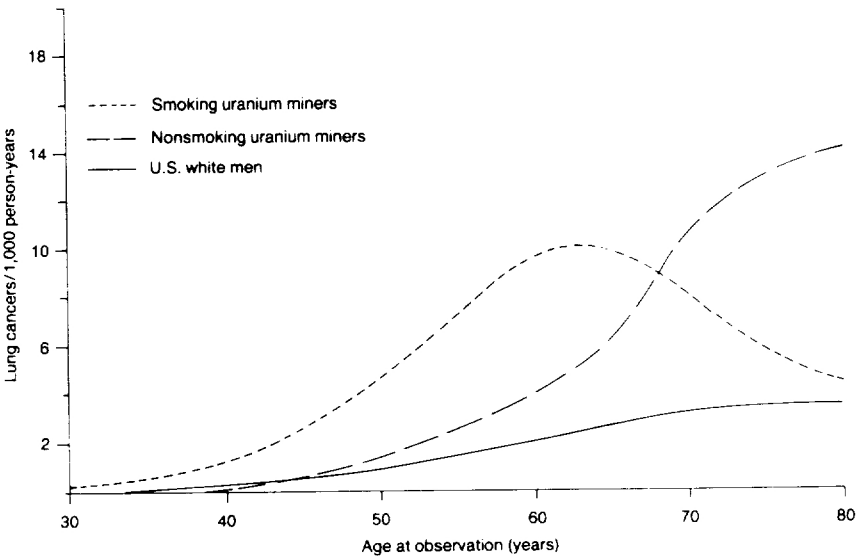

FIGURE 3.—Hypothetical lung cancer distribution among smoking and nonsmoking uranium miners with uniform radon daughter exposure and among U.S. white men

radiation and CSC were applied periodically (both separately and together) so that large total doses of both were used. The first report gave results at 18 months and considered the interaction to be synergistic. Fifty-four percent of the mice with combined agents had skin cancer versus 37 and 5 percent, respectively, when the agents were used singly. However, when the study was completed by following the mice until they died naturally, the sum of the skin cancers among the groups treated with single agents was nearly as large as the number found among the mice treated with both agents. Cancers appeared 6 to 7 months earlier in mice treated with both agents.

A preliminary experiment using CSC and beta particles on rat skin (McGregor 1976) found a threefold increase in skin tumors over that induced by beta radiation alone. The effect was attributed to tumor promotion activity because the CSC applications were started 2 months after beta exposure and because the amount of CSC used did not produce any tumors when used alone. This was followed by further experiments (McGregor and Meyers 1982), using 916 rats. CSC was applied immediately after exposure to 1,600 rad of beta

particles in one group and 2 months after in another group. When applied immediately, severe ulceration resulted, making tumor yield difficult to interpret. When applied 2 months after radiation, malignant and nonmalignant yields were increased ($p < 0.01$). Again, the levels of CSC used produced no significant increase in cancers by themselves. The experiments were terminated at 14 and 18 months, so the ultimate cancer yields were not determined, but at the end of the experiment there were 2.5 times as many cancers in the beta-plus-CSC group as in the beta-alone group. At 50 weeks, however, the ratio was higher (3.4), indicating that tumors appeared earlier in the group treated with both agents.

Nenot (1977) studied rats that inhaled cigarette smoke plus americium 241, which delivered alpha radiation to the lungs. The smoke increased the yield of lung cancers and made them appear earlier. It was interpreted as a cancer-promoting effect by cigarette smoke, because the smoke alone did not produce cancer at the doses used.

The carcinogenic effects of radon daughters, uranium ore dust, and cigarette smoke in dogs have been reported (Cross et al. 1978, 1982; NCRP 1984b). Dogs were exposed to radon daughters plus uranium ore dust, to radon daughters plus ore dust plus cigarette smoke, to cigarette smoke alone, or to sham cigarettes with room air. Daily cigarette smoking periods both preceded and followed the dust plus radon daughter exposures. There were seven lung cancers among the 20 nonsmoking dogs and none among the controls or the dogs exposed to smoke alone. Although no dogs were exposed to dust alone, other experiments suggest that they would not have developed lung cancer. Exposure to 20 cigarettes per day resulted in pulmonary emphysema and fibrosis. These two conditions, however, were much more severe in the dogs exposed to mixtures that included radon daughters and uranium ore dust. Two nasal carcinomas were found in the dogs exposed to ore dust and radon daughters, and one in the group exposed to these two agents plus smoke. There were none in the other two groups. In these studies, cigarette smoke appeared to be protective.

In an extensive series of experiments in France, cigarette smoke was inhaled by rats, either before or after a series of radon daughter inhalations (Chameaud et al. 1980, 1981, 1982). The cigarette smoke alone did not produce lung cancers at the levels used. When the smoke was given in the weeks preceding radon daughter inhalation, it had no effect; when the exposure to smoke was delayed until after radon daughter exposure was completed, or given during radon daughter exposure, significantly higher numbers of lung cancers were observed. These features were considered to be characteristic of cancer promotion by cigarette smoke, although the terms "cocarcinogenesis" and "synergism" were at times applied by the researchers.

Interactions of Radiation and Chemical Carcinogens

A number of experiments tested the interaction of radiation and chemical carcinogens. Some of these chemicals are constituents of cigarette smoke or are chemically related to such constituents. Although most carcinogens can also act as cancer-promoting agents, in these experiments the additional tumor promoters in cigarette smoke were absent, making them less pertinent to the topic of radiation and cigarette smoke interaction than the experiments reviewed in the preceding section. With this in mind, they are summarized below. Benzo[a]pyrene (BaP) and polonium 210 (Po-210) were injected intratracheally in hamsters (McGandy et al. 1974; Little and O'Toole 1974; Little et al. 1978). When given simultaneously, tumors appeared earlier, but the effects were additive. When BaP was given 4 to 5 months after radiation, the effects appeared to be synergistic, but because effects were small when BaP was given first and saline injections had nearly the same effect, the BaP action was considered to be mostly tumor promotion. A similar study with intratracheal instillations of BaP and plutonium oxide (PuO_2) was done in rats (Metivier et al. 1984) and was considered to show synergism. Both PuO_2 and Po-210 emit alpha particles.

BaP used with 150 roentgens of whole body x ray on mouse fetuses resulted in more tumors (of all types) than was obtained with x ray alone, but fewer than was obtained with the BaP alone (Urso and Gengozian 1982).

Dimethylbenz[a]anthracene (DMBA) and 0.8 MeV electrons were administrated to rat skin at 28 days of age (Burns and Albert 1984). Multistage analysis of the interaction suggests the existence of two dose-dependent stages for single doses of radiation and multiple doses of DMBA, and also that prolongation of the radiation dose either adds four presumably non-dose-dependent stages or stimulates clonal growth of an early stage cell.

Rats were given 600 WLM, then treated with 5-6 benzoflavone, methylcholanthrene (MCA), or phenobarbital (Queval et al. 1979). MCA is a carcinogen, the other two are not. Phenobarbital had no effect. With both benzoflavone and MCA the number of tumors was doubled. The latent period was greatly shortened with benzoflavone, but only slightly with MCA. Benzoflavone suppresses tumor development when used with BaP.

When rat fetuses were exposed to x ray and the mothers were injected with ethylnitrosourea (ENU) 4 days later, as adults the rats developed fewer neurogenic tumors than with ENU alone. This reduction in tumors was not due to an increased mortality rate of the fetally exposed animals (Kalter et al. 1980).

The administration of 1.25 gray (Gy) whole body x ray followed by injection of ENU was used to induce nervous system tumors (Knowles 1982). The incidence of these tumors was consistently and

significantly higher in the group given ENU alone than in any of the irradiated groups. The histology of tumors in all groups resembled those induced by ENU.

When mice were irradiated in utero (36 rad x ray) and then given urethane at 21 days of age, the yield of lung tumors was enhanced over urethane alone (Nomura 1984). X ray alone yielded no tumors. The x-ray effect was seen during the first 14 days of gestation, but not during the later fetal or neonatal stages.

Intraperitoneal application of tetradecanoylphorbol acetate (TPA) (a strong tumor-promoting agent) had no influence on the incidence of malignant lymphomas following four doses of 1.7 Gy of x ray (Brandner et al. 1984).

When beta particles from phosphorus 32 were used with TPA and high fat, high protein diets as potential tumor-promoting agents, no evidence of tumor promotion was found on liver cell transformation (Berry et al. 1984).

Comment on Animal Studies

Although the results of the animal studies indicate that the interaction between radiation and cigarette smoke, or its components, ranges from no interaction to protection, promotion, and synergism, there are several features common to many of the experiments. When cigarette smoke or BaP is administered before the radiation, there is little or no interaction with respect to tumors. When administered several months after the radiation, the interaction is greater. In addition, as a general rule, tumors appear earlier in animals when cigarette smoke is used. In some of the experiments, the early appearance of cancers caused investigators to apply the word "synergism" to the interaction, but further followup plus the production of few or no cancers by the smoke or CSC alone, usually led the investigators to conclude that the interaction was mainly one of cancer promotion (Chameaud et al. 1981; McGregor and Meyers 1982). Some of the experiments with cigarette smoke components led to the same conclusion (Little et al. 1978). This conclusion is buttressed by the observation that the cancer-promoting activity of cigarette smoke is greater than its initiating activity (Bock 1968, 1972; Van Duuren et al. 1971; Wynder 1983). Cancer promoters sometimes increase the yield of cancers in animal experiments by simply speeding up the appearance of the tumors. Nonspecific injury sometimes promotes radiation-induced tumors.

Polonium 210 in Cigarette Smoke

Lead 210, which has a 22 year half life, is widely deposited on plant foliage as a result of radon and radon daughter decay in the atmosphere. It decays slowly to Po-210, which emits alpha particles

that are more dangerous than the beta particles emitted by lead 210. Appreciable amounts of these two radioisotopes are found in tobacco and in tobacco smoke, and may contribute to the cancer potential of cigarette smoke (Radford and Hunt 1964; Kolb et al. 1966; Stahlhofen 1968; Black and Bretthauer 1968). A major fraction of the inhaled Po-210 was shown to be absorbed from the lung directly into the bloodstream (Little and McGandy 1968). Intratracheal instillation of Po-210 into the lungs of hamsters resulted in cancer at levels as low as 15 rad (Little et al. 1978). Calculations of the radiation dose from the Po-210 in cigarettes have been made repeatedly. Doses to small portions of the bronchial epithelium were found in man to be about 1 rad per year (Cohen et al. 1980), 8 rem per year (Steinfeld 1980), and 80 to 100 rad per lifetime (Martell 1983). Average exposures to the bronchial epithelium, however, are much less than these calculated doses, which are administered to very small selected spots. There has been considerable debate as to how much the radiation from Po-210 contributes to the lung cancer that results from smoking, ranging from no effect (Hickey and Clelland 1982) to most of the cancers (Wagner 1982; Ravenholt 1982; Martell 1983; Winters and Di Frenza 1983). The consensus appears to reflect a middle ground—that the radiation in cigarette smoke contributes to its carcinogenicity, but that the chemical agents in smoke also contribute (Radford 1982; Cross 1984).

To the extent that Po-210 in cigarette smoke induces lung cancer, its effect would be expected to be directly additive to the effect of the short half-life radon daughters. To the extent that chemical agents are involved (either as cancer initiators or as promoters), an interaction might be expected to occur. Both the animal data and the human data reviewed indicate at least some interaction, which therefore reflects action by the chemical constituents of cigarette smoke, particularly as promoters.

Hypothesis That Reconciles Discrepancies in Epidemiological Data

A hypothesis that could reconcile the discrepancies in the epidemiologic data has been presented (Archer 1985). Alpha radiation dose from radon daughters may induce a finite number of lung cancers in an irradiated group, with most of these cancers being expressed. In the absence of cigarette smoking, these cancers could have a longer latent period and may or may not be fully expressed among the population, depending on the force of competing causes of death among the older members of the population and the presence or absence of promoting agents. In the presence of continuing exposure to cigarette smoke, these radiation-induced cancers could appear at

an earlier date following exposure (and at younger ages) than among groups not exposed to cigarette smoke.

The lung cancers that would normally be induced by cigarette smoke would still be present, and added to those induced by radiation in a mining population. Thus, on a lifetime basis, there would appear to be an additive effect (radiation plus smoking), plus perhaps a few extra cancers that would not have been expressed if the latent period had not been shortened by smoking. The earlier appearance of cancers among smokers would give an appearance of synergism in studies conducted within 20 or 30 years after the start of exposure.

This hypothesis is best understood by examining Figure 3. In this hypothetical graph it is assumed that an equal number of smoking and nonsmoking miners of the same age are exposed at age 30 to the same amount of radon daughters. The resultant curves of lung cancer incidence reflect the distribution in time of the appearance of the induced cancers. The shape of the curves might vary somewhat from the curves for people who are first exposed at older ages. It is evident from these curves that investigators who examine lung cancer mortality data at different points in time after the subjects had begun mining could obtain data indicating synergism (at 40 to 60 years of age), or additivity (at 60 to 70 years of age), or protectiveness (at 70 or more years of age). The "synergism" noted in the U.S. uranium miner studies (mean age at death was 55 years for nonsmokers) would thus be explained (Saccomanno et al. 1967), as would the "protection" found in one of the Swedish studies (mean age at death was 70 years for nonsmokers) (Axelson and Sundell 1978). The "additive" effect noted by another Swedish study (mean age at death was 65 years) with deaths collected over a 26-year period (Radford and Renard 1984) would also be explained. The long data-gathering period resulted in a collection of deaths from young as well as aged miners. The short collection period used in another Swedish study (Damber and Larsson 1982) (mean age at death was 69 years), interpreted as "synergism," may have resulted from a biased sampling of deaths because they were from a 5-year period only, or were from the entry into mining at different times or ages by smokers and nonsmokers.

A mortality analysis of radon daughter-exposed miners within 25 years after they started mining would, according to the hypothesis, give an early impression of synergism, just as early observations in two of the animal studies did (Suntzeff et al. 1959; McGandy et al. 1974), even though lifetime studies would indicate otherwise.

According to some experts, even if the final incidence of lung cancer in smoking and nonsmoking irradiated individuals were the same, the net effect could be regarded as synergistic; this is because

smoking shortens the tumor-free life of those who develop cancer (UN Sci. Comm. 1982).

Interaction of Radiation and Cigarette Smoke on Other Aspects of the Respiratory Tract

Larynx and Nasal Sinuses

The attachment of radon daughters to dust particles that are deposited in the airways (along with unattached ions) of animals and man means that the upper respiratory tract and bronchi receive higher total doses of radiation than any other part of the body. Excess cancers of the larynx have been reported in uranium miners (Tichy and Janisch 1973). Although this cancer site has been associated with cigarette smoking, the possible interaction of the two agents on the larynx has not been evaluated. Cancer of the sinuses has been attributed to the radon and radon daughters that collect in the paranasal sinuses of people with elevated radium body burdens (Rowland et al. 1978; Schlenker and Harris 1979). Cancer of these sinuses has not been attributed to cigarette smoke in U.S. populations. The nasal and pharyngeal and tracheal epithelium in man may be sufficiently thick and covered by enough protective mucus so that the alpha particles from radon daughters rarely penetrate to those cells where permanent injury can result (presumably the basal germinal layer). The thin epithelium of the bronchial subdivisions apparently may not provide similar protection.

Pulmonary Function and Fibrosis

Epidemiologic studies have demonstrated that the pulmonary function of uranium miners is compromised (Archer, Carroll et al. 1964; Archer, Brinton et al. 1964; Trapp et al. 1970; Samet, Young et al. 1984). The loss in pulmonary function is followed in time by greatly elevated mortality rates from or with nonmalignant pulmonary disease (Archer et al. 1976; Archer 1980; Waxweiler et al. 1981). In these analyses several diseases were grouped together—cor pulmonale, silicosis, pulmonary fibrosis, chronic obstructive lung disease, emphysema, and related diagnoses—because diagnostic criteria for them are known to vary greatly between physicians. They usually reflect injury by inhaled toxic agents. Uranium miners were also exposed to a third toxic agent, silica (alpha quartz), in ore dust as well as to radon daughters and cigarette smoke.

Uranium ore dust and tobacco smoke, as well as radiation, undoubtedly contribute to the nonmalignant pulmonary problems of uranium miners. Both human studies and animal studies have indicated that radiation contributes to the lung pathology and functional loss (Archer, Brinton et al. 1964; Cross et al. 1978; Cross, Filipy et al. 1981; Cross, Palmer et al. 1981). Very few of the uranium

miners disabled by shortness of breath had typical silicotic nodules on x ray and were therefore unable to obtain workmen's compensation for silicosis. Neither the relative roles nor the interactions of these three agents (radon daughters, cigarette smoke, silica) in these conditions is well characterized.

The pathology of radiation pneumonitis after larger acute radiation doses is well known (Gross 1981). Following irradiation at high doses, there is death of some of the epithelial and endothelial cells within 3 to 6 months, resulting in increased capillary permeability and leakage of plasma proteins into the alveolar surface. Within 1 to 3 years, the pneumonitis is followed by a fibrotic reaction, which may represent a healing of the radiation pneumonitis, but has the effect of reducing the functional capacity and compliance of the lung.

After relatively low chronic doses of alpha radiation, as occurs in uranium miners, such changes have not been reported, but some fibrotic change is implied by the aforementioned epidemiologic studies. The high linear energy transfer of alpha radiation leads to the belief that cellular injury and repair after chronic low doses of alpha radiation could slowly lead to fibrotic changes. The injury would be so diffuse, however, that fibrosis would be detectible only after many years. Loss of pulmonary function, fibrosis, and other changes have been observed in the lungs of rats, hamsters, and dogs chronically exposed to radon daughters, cigarette smoke or diesel exhaust, and uranium ore dust (Gaven et al. 1977; Stuart et al. 1977, 1978; Wehner et al. 1979; Cross, Palmer et al. 1981; Cross, Filipy et al. 1981; Cross et al. 1982; NCRP 1984b). Although these experiments were not designed to evaluate the degree of interaction of the different agents, it was clear that the fibrotic and other pathologic changes were much more severe when the animals were exposed to two or three of the agents together than when exposed to a single agent.

The relatively low radon daughter exposures at which pulmonary function effects (possibly due to radiation) have been found in uranium miners (Samet, Young et al. 1984) suggest that there may be no threshold for such effects.

Research Recommendations

1. The possibility that alpha radiation from background radon daughters in homes may contribute to lung cancer in human populations (Axelson 1983; NCRP 1984a, b; Harley 1984; Radford and Renard 1984) and the interaction of both active and involuntary tobacco smoking on this possible effect of radon daughters need further investigation. They may have important implications for the ventilation of homes and for the effects of involuntary smoking.

2. The influence of tumor-promoting agents on radiation-induced cancers has not been adequately explored. Further animal studies of this interaction are indicated.

Summary and Conclusions

1. There is an interaction between radon daughters and cigarette smoke exposures in the production of lung cancer in both man and animals. The nature of this interaction is not entirely clear because of the conflicting results in both epidemiological and animal studies.
2. The interaction between radon daughters and cigarette smoke exposures may consist of two parts. The first is an additive effect on the number of cancers induced by the two agents. The second is the hastening effect of the tumor promoters in cigarette smoke on the appearance of cancers induced by radiation, so that the induction-latent period is shorter among smokers than nonsmokers and the resultant cancers are distributed in time differently between smokers and nonsmokers, appearing earlier in smokers.

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CHAPTER 12

SMOKING INTERVENTION PROGRAMS IN THE WORKPLACE

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